DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: MAR 12 2004 March

From: Division of Dietary Supplement Programs , Office of Nutritional Products, Labeling and Dietary Supplements, HFS-810

Subject: 75-Day Premarket Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305

Subject of the Notification: BSP-201

Firm: Cantox

Date Received by FDA: Dec. 04, 2003

90-Day Date: March 05, 2004

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification and related correspondence for the aforementioned substance should be placed on public display in docket number 95S-0316 as soon possible since it is past the 90-day date. Thank you for your assistance.

Tanya L. Jackson Ph.D

95S-0316

RPT222

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service
Food and Drug Administration
College Park, Maryland 20740

FEB 17 2004

David H. Bechtel, Ph.D., DABT
CANTOX
Health Sciences International
1011 U.S. Highway 22, Suite 200
Bridgewater, New Jersey 08807-2950

Dear Dr. Bechtel:

This is to inform you that the notification, dated December 3, 2003, you submitted on behalf of your client, BSP Pharma A/S ["BSP Pharma"] of Copenhagen, Denmark, pursuant to 21 U.S.C. 350b(a)(2)(section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)) was filed by the Food and Drug Administration (FDA) on December 4, 2003. Your notification concerns the substance called BSP-201, a purified extract from the nut of *Butyrospermum parkii* Kotschy (shea nut tree), that you intend to market as a new dietary ingredient.

The notification informs FDA that "BSP Pharma" intends to use BSP-201 in dietary supplement formulations. According to the notification, BSP-201 will be encapsulated in gelatin. Each capsule will contain 750 mg of BSP-201 including 50% unsaponifiable matter. The recommended intake is four capsules twice daily representing a maximum daily intake of 6.0 g of BSP-201.

In accordance with 21 C.F.R.190.6(c), FDA must acknowledge its receipt of a notification for a new dietary ingredient. For 75 days after the filing date, your client must not introduce or deliver for introduction into interstate commerce any dietary supplement that contains BSP-201.

Please note that acceptance of this notification for filing is a procedural matter and, thus, does not constitute a finding by FDA that the new dietary ingredient or supplement that contains BSP-201 is safe or is not adulterated under 21 U.S.C. 342. FDA is not precluded from taking action in the future against any dietary supplement containing BSP-201 if it is found to be unsafe, adulterated, or misbranded.

Your notification will be kept confidential for 90 days after the filing date of December 4, 2003. After the 90-day date, the notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. Prior to that date, you may wish to identify in writing specifically what information you believe is proprietary, trade secret or otherwise confidential for FDA's consideration.

Should you have any questions concerning this matter, please contact Victoria Lutwak at (301) 436-2375.

Sincerely yours,

Linda J. Bellucci for

Susan J. Walker, M.D.
Director
Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

CANTOX
HEALTH SCIENCES INTERNATIONAL

1011 U.S. Highway 22, Suite 200
Bridgewater, New Jersey 088072950
Phone: (908) 429-9202
Fax: (908) 429-9260

December 3, 2003

Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Pkwy
College Park, MD 20740

RE: New Dietary Ingredient Notification

Dear Sir or Madam:

On behalf of BSP Pharma A/S ["BSP Pharma"], we submit the attached information pursuant to section 413(a) of the Federal Food, Drug, and Cosmetic Act, in support of BSP Pharma's marketing of the new dietary ingredient BSP-201, a Shea Butter extract containing 25% unsaponifiable matter. The enclosed information is a resubmission and clarification of a previously submitted New Dietary Ingredient Notification. BSP Pharma intends to market this ingredient for dietary supplement use.

Respectfully submitted,

David H. Bechtel, Ph.D., DABT
Senior Scientific Consultant

Enclosure

CANTOX
HEALTH SCIENCES INTERNATIONAL

Facsimile Transmittal

To:	Vicky Lutwak	**Fax:**	301-436-2636
From:	Erica Rath	**Date:**	December 4, 2003
Re:	BSP-201 Cover Letter	**Pages:**	2
CC:		**Project:**	N/A

Original sent *via* ☐ **courier** ☐ **mail** ☒ **faxed only**

– CONFIDENTIAL –

Vicky,

Per your discussion with Dr. David Bechtel, please see the revised cover letter for the New Dietary Notification for the BSP-201product containing 50% unsaponifiable material. We thank you for bringing this matter to our attention. If there is anything else you need please do not hesitate to contact us.

Thank you,

Erica Rath

Erica Rath
Toxicologist
Cantox U.S. Inc
1011 US Highway 22W.,
Suite 200
Bridgewater, NJ 08807-2950
Phone: (908) 429-9202
Fax: (908) 429-9260

NOTE: If there were any problems with this transmission or if the addressee is not at this number, please call our office at (908) 429-9202. Our Facsimile number is (908) 429-9260.

CANTOX
HEALTH SCIENCES INTERNATIONAL
1011 U.S. Highway 22, Suite 200
Bridgewater, New Jersey 08807-2950
Phone: (908) 429-9202
Fax: (908) 429-9260

December 4, 2003

Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Pkwy
College Park, MD 20740

RE: New Dietary Ingredient Notification

Dear Sir or Madam:

On behalf of BSP Pharma A/S ["BSP Pharma"], we submit the attached information pursuant to section 413(a) of the Federal Food, Drug, and Cosmetic Act, in support of BSP Pharma's marketing of the new dietary ingredient BSP-201, a Shea Butter extract containing 50% unsaponifiable matter. The enclosed information is a resubmission and clarification of a previously submitted New Dietary Ingredient Notification. BSP Pharma intends to market this ingredient for dietary supplement use.

Respectfully submitted,

David H Bechtel

David H. Bechtel, Ph.D., DABT
Senior Scientific Consultant

Enclosure

SECTION 1

The name and complete address of the manufacturer of the dietary supplement that contains the dietary ingredient, or the dietary ingredient.

The manufacturer of the dietary ingredient will be:

BSP Pharma A/S
Box 115
Fruebjergvej 3
DK- 2100 Copenhagen, Denmark

Attention: Tonny Jørgensen
Chief Executive Officer

SECTION 2

The name of the dietary ingredient.

The dietary ingredient is BSP-201, a Shea Butter extract containing 50% unsaponifiable matter.

BSP-201 is a purified substance produced from sheanut oil obtained from the nut of the *Butyrospermum parkii* tree. BSP-201 is processed using standard procedures used in the edible oil industry, including extraction, deacidification, and decolorization, followed by fractionation into shea stearine and shea oleine. Shea oleine, which is high in unsaponifiable matter (~10%) and is used largely as cooking oil, undergoes further processing, including dekaritenization, washing with NaOH solution, salt water, and process water, bleaching, interesterification, and hydrogenation. Additional fractionation results in a fraction with approximately 50% unsaponifiable matter, which is subsequently washed, deodorized, and supplemented with a natural food-approved antioxidant. All additives and solvents used in the processing of BSP-201 are of food- or pharmaceutical-grade. The primary components of BSP-201 include the unsaponifiable material (esterified triterpene alcohols and sterols; 50-55%), diglycerides and triglycerides (40-55%), cinnamic acid and hydrogenated cinnamic acid (1-4%), kariten (1-3%), free sterols, free triterpene alcohols, and some other minor components (0-1%), and free fatty acids (0.05-0.20%).

SECTION 3

Description of the dietary supplement or dietary supplements that contain the dietary ingredient including (i) the level of dietary ingredient in the dietary supplement, and (ii) the conditions of use recommended or suggested in the labeling of the dietary supplement, or if no conditions of use are recommended or suggested in the labeling of the dietary supplement, the ordinary conditions of use of the supplement.

The BSP-201 shea butter extract with 50% unsaponifiable matter dietary ingredient will be marketed for use in products meeting the definition of "dietary supplement" in section 201(ff) of the Federal Food, Drug, and Cosmetic Act. The BSP-201 shea butter extract with 50% unsaponifiable matter dietary ingredient will be clearly labeled and promoted as a dietary supplement. The dietary ingredient will be encapsulated in gelatin or starch, and each capsule will contain 750 mg of BSP-201 (325 mg of unsaponifiable matter). Consumption of 4 capsules twice a day will be suggested or recommended, resulting in a maximum daily consumption of 6.00 g of BSP-201 (3.00 g unsaponifiable matter/day, or approximately 60 mg/kg body weight for a 50 kg person).

SECTION 4

The history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe, including any citation to published articles or other evidence that is the basis on which the distributor or manufacturer has concluded that the dietary supplement will reasonably be expected to be safe.

The overall safety of BSP-201 is supported in part by the long-time presence of its source food substance, sheanut oil, in the human diet. Sheanut oil has a long history of use as a cooking oil in Africa, and in Europe, substances derived from the oil have been used since the 1800's for various cooking purposes. There are no documented adverse effects from food use of sheanut oil, and the United States Food and Drug Administration affirmed that the use of refined sheanut oil as a direct human food ingredient was generally recognized as safe in accordance with 21CFR184.1702.

Though BSP-201 has a much higher concentration of unsaponifiable matter (~50%) than sheanut oil (2-17% unsaponifiable matter) and substances derived from sheanut oil, and has no history of human use *per se*, the widespread use of shea oleine (~10% unsaponifiables), a further refined sheanut oil, in baked goods and other foods in Europe indicate safe intake of approximately 3 g/day of unsaponifiable matter. In addition, the safety of BSP-201 is supported by both unpublished data from preclinical studies of BSP-201 sponsored by the dietary ingredient's manufacturer as well as safety data from studies of other substances derived from sheanut oil published in peer-reviewed scientific journals.

As shown in Table 1, which details the relative composition among classes of sheanut oil unsaponifiables as reported in the published scientific literature, sheanut oil unsaponifiables are comprised primarily of triterpene alcohols (~95%). Sterols and 4-methylsterols are also present but in lesser amounts. The triterpene alcohols, which are also designated as 4,4-dimethylsterols, also comprise the unsaponifiable fraction of BSP-201. It is these chemical similarities between the unsaponifiable matter in shea oleine and sheanut oil-derived fractions that justify the use of pre-clinical and clinical studies of these materials, when viewed on the basis of the intake of sheanut oil unsaponifiable matter rather than on the intakes of the sheanut oleine or other sheanut oil-derived fractions themselves, as the basis for the conclusion that the use of the BSP-201 dietary ingredient according to conditions of use recommended or suggested in the labeling of the dietary supplement, which would result in a maximum daily intake of 3.0 g/day of unsaponifiable matter, a level that can reasonably be expected to be safe for a 70-kg adult based on the available data.

reported, were undoubtedly present in the unsaponifiable fraction of shea oleine and sheanut oil that were tested previously and found to be safe. Moreover, as detailed in this section, the safety of the present triterpene products has been confirmed through direct testing of the preparation.

In an unpublished acute toxicity study of the BSP-201 preparation with 50% unsaponifiable matter carried out in Wistar rats as recommended in the Organization for Economic Co-operation and Development (OECD) guidelines for acute oral toxicity testing, single gavage doses of 2000 mg BSP-201/kg body weight (b.w.), equivalent to 1000 mg unsaponifiable matter/kg b.w., were administered to male and female rats (5/sex); animals were observed for at least 1, 3, and 6 hours after dosing and daily thereafter for 14 consecutive days. There were no deaths or other signs of toxicity and body weight gains were normal during the study period. Piloerection was observed in 3 animals 1 hour after treatment and in five animals 3 hours after treatment, though the authors suggested this may have been related to treatment and handling procedures. Erythema was observed in the intestine of one male and discoloration of the liver, spleen, and lungs was seen in one female during gross necropsy examination. The authors concluded the minimal lethal dose was above 2000 mg BSP-201/kg b.w. or 1000 mg unsaponifiable matter/kg b.w.

SBE C-80 FA, a material containing 75% unsaponifiable matter and composed of the same triterpenes and same fatty acid esters as BSP-201, was tested for ulcerogenic effects in rats in an unpublished study. Twelve Sprague-Dawley rats were administered 2000 mg/kg doses of SBE C-80 FA dissolved in arachid oil by oral gavage daily for four days. Other rats were doses with the control vehicle or with 200 mg/kg of ibuprofen, which served as a positive control. Following an overnight fast, the rats were received intravenous injections of 1 ml of % Evans blue saline 30 minutes prior to sacrifice. The stomach and small intestines were scored for gastrointestinal lesions. No adverse clinical signs were recorded, and no adverse effects on body weight were seen with the exception of one rat treated with ibuprofen. No gastrointestinal lesions were observed in control rats or in rats treated with the test material. In contrast, a significant number of lesions were observed in rats treated with ibuprofen as compared to those in the control group($p=0.0018$ for gastric lesions, $p<0.0001$ for intestinal lesions). The majority of these small intestinal lesions were seen in the aboral part of the jejunum and in the ileum. SBE C-80 FA, at oral doses of 2000 mg/kg/day administered for 4 days, was found to have no ulcerogenic effect in the rat. This lack of gastrointestinal effects, along with the absence of treatment-related adverse clinical signs, supports the safety of short term (4 day) intake of up to 1500 mg/kg of unsaponifiable matter.

The genotoxicity of BSP-201 was evaluated in two unpublished studies sponsored by the manufacturer, namely an Ames bacterial mutagenicity assay an in an *in vivo* mouse micronucelus test. Both studies were conducted according to the methods of the OECD. In the Ames assay, BSP-201 in dimethylsulfoxide (DMSO) was not toxic to *Salmonella typhimurium* strains TA102, TA100, TA98, TA1537, or TA1535 at dose levels of 50, 160, 500, 1600 and 5000 μg/plate. In addition, no biologically or statistically significant increases in the number of revertant colonies were observed in any tester train after

treatment with BSP-201 at any dose level, either in the presence or absence of rat liver metabolic fraction (S-9), as compared with negative controls.

In the *in vivo* mouse micronucleus assay, male mice were treated with a single dose 2000 mg/kg b.w. dose of BSP-201 or controls by oral gavage. Five mice from each group were sacrificed 24 hours after dosing while five additional mice from the BSP-201 and the negative control groups were sacrificed 48 hours after dosing. No adverse reactions to BSP-201 treatment were observed, nor were any biologically or statistically significant increases in the frequency of micronucleated polychromatic erythrocytes in mice treated with BSP-201 as compared with negative controls. It was concluded that BSP-201 was not genotoxic under the conditions of this study.

In a pharmacological study of BSP-201 conducted by the manufacturer of the dietary ingredient to assess the anti-inflammatory activity via the carrageenan-induced paw edema assay, significant anti-inflammatory activity was reported but no adverse clinical signs were observed in male Sprague-Dawley rats (10 animals/group) treated with the test material at the 125, 250, 500, or 1000 mg/kg b.w. dose levels by oral gavage.

The subchronic toxicity of crude shea oleine and hardened (i.e., hydrogenated) refined shea oleine was evaluated in a study published by Earl *et al.* (2002). Wistar rats (15 males and 15 females) received 27.5% total fat semipurified diets containing 20% (w/w) crude shea oleine and hardened (i.e., hydrogenated) refined shea oleine, along with palm and soyabean oils. The actual intake of shea oleine from the two diets was found to be about 10 to 15 g/kg/day, and given the reported 7.44% and 6.52% unsaponifiable material of the shea oleine and the hardened shea oleine (comprised of approximately 97% 4,4-dimethylsterols, 2% 4-demethylsterols, and 0.5% 4-α-methylsterols), it is estimated the rats consumed approximately 0.7 to 1.1 g/kg b.w./day of unsaponifiable material.

The findings of this study indicated that the feeding of shea oleine in the diet was associated with only slight reductions in body weight gains, small increases in food intake, and some minor changes in clinical chemistry and histopathology. Most of these changes were considered to be related to high dietary fat content and/or were deemed inconsequential to normal growth. The authors concluded that based on these findings, shea oleine given at 20% of the diet (10 to 15 g/kg/day, equivalent to levels of up to 1.1 g/kg b.w./day of unsaponifiable matter) was well tolerated and appeared to have no adverse effect on the growing rat. A 50 kg body weight person using BSP-201 in accordance with the dosing recommendations is expected to consume, at most, 0.060 g/kg b.w./day of unsaponifiables.

Baldrick *et al.* (2001) conducted 2 studies to investigate the reproductive toxicity potential of shea oleine following dietary administration to rats during pre-mating, mating, pregnancy and offspring weaning. The studies compared 7 or 15% (w/w) hardened shea oleine with 7 or 15% (w/w) of the unhardened material (approximately equivalent to 3.5 or 7.5 g/kg/day); additionally toffee powder and cocoa butter (STUDY 1), and sheanut, unhardened palm oil and hardened palm oil (STUDY 2) were used for comparison. Toffee powder was selected for comparison in STUDY 1 since, at the time,

it was a commercially available material comprised of 20% hardened shea oleine. The authors note that since STUDY 1 and STUDY 2 were conducted a number of years apart, different comparator oils were employed in each; thus, a direct comparison between studies was not feasible.

Though the STUDY 1 diets were not analyzed, analysis of STUDY 2 diets revealed the levels of unsaponifiable material in the crude sheanut oil, shea oleine, and hydrogenated shea oleine to be 5%, 6.4%, and 3.5%, respectively, as compared to 0.1% for both the palm oil and the hardened palm oil. Te unsaponifiable material in the shea test materials consisted primarily (~96%) of 4,4-dimethylsterols, with lesser amounts of 4-demethylsterols (~3.4%) and 4-α-methylsterols (~0.8%). It can be estimated that animals consuming 7.5 g shea oleine/kg/day would have consumed up to 0.48 g/kg b.w./day (6.4%) of unsaponifiable matter.

In STUDY 1, groups of Colworth-Wistar rats (n=40; 20 animals/sex) received diets containing 7% (w/w) of shea oleine, 7% (w/w) of a hydrogenated ('hardened') shea oleine, 7% (w/w) of cocoa butter or 35% (w/w) of toffee powder for 20 consecutive weeks. During week 12 of the 20-week feeding period, rats were mated, and following gestation, all dams were allowed to litter. At weaning, offspring were fed the parental diet for 7 to 10 days prior to sacrifice. In addition, 12 male and 12 female parental animals from each group were sacrificed following the 20-week treatment period (after weaning) for examination. Parental animals were assessed for general condition and health, body weights, food consumption, clinical pathology evaluation, gross necropsy examination and weighing of selected organs while assessment of pups included a clinical chemistry evaluation, as well as skeletal (using X-ray) and macroscopic examinations. In STUDY 2, groups of Colworth-Wistar rats (n=100; 50 animals/sex) received diets containing 15% (w/w) of sheanut oil, shea oleine or palm oil, or 15% (w/w) of a hydrogenated ('hardened') shea oleine and palm oil, for 10 consecutive weeks. Experimental diets were introduced 2 weeks prior to mating; dams were allowed to litter and at weaning, offspring were fed the parental diet. Endpoints observed included assessment of general health and measurement of litter and weaning parameters. In addition, at the end of the 10-week treatment period, liver, lymph glands, serum and red blood cells were examined for fatty acid composition, and livers and mesenteric lymph nodes were examined for evidence of lipogranulomas in F_0 animals.
For parental animals, results from STUDY 1 indicated that there were no differences in the general condition of animals fed the 4 diets. Actual test material intake ranged from 3 to 6 g/kg/day across the groups. Compared to rats fed the cocoa butter diet, a statistically significant reduction in mean body weight gain was observed in males receiving unhardened shea oleine and in both sexes receiving toffee powder; a marginal but statistically significant increase in body weight gain was noted in females fed the unhardened shea oleine diet. In contrast, the hardened shea oleine diet elicited no effect on body weight gains. The authors attributed the observed reduction in body weight gain to a reduced calorific value of the shea oleine diets.

No differences in hematological parameters were noted among the groups after 20 weeks of treatment. Results of clinical chemistry analyses showed a trend for reduced mean

cholesterol in both sexes fed the unhardened shea oleine, toffee powder and hardened shea oleine diets, compared to those receiving cocoa butter. Increased mean alkaline phosphatase (ALP) values were also observed in both sexes of the unhardened shea oleine, hardened shea oleine and toffee powder groups. The authors suggest both findings resulted from the feeding of high fat diets. With respect to organ weights, an increase in the absolute mean heart weights of females fed the unhardened and hardened shea oleine diets, compared to those receiving the cocoa butter diet, was observed. In offspring, none of the diets had an effect on the number of litters born or weaned. Litter size, number of pups at birth and weaning, survival and body weight at weaning were similar among groups. Results of clinical chemistry analyses showed an increase in mean ALP values for both sexes in the hardened shea oleine and toffee powder groups; a smaller increase was also observed in the unhardened shea oleine group. Macroscopic and x-ray examination of animals showed no findings related to the test materials.
For parental animals in STUDY 2, no unusual health problems were noted. Results from fatty acid analyses of the liver, lymph node and blood serum, as well as the membrane phosphatidyl choline (PC) analyses showed no unexpected results for the diets administered. Likewise, histopathological examination of the liver and mesenteric lymph nodes showed no evidence of lipogranulomas in any of the groups. For offspring, none of the diets had any effect on the number of litters born. No significant differences were noted in pup body weights at birth and weaning among groups.

Based on the results of STUDY 1 and STUDY 2, the authors concluded that there was no evidence of reproductive toxicity for unhardened or hardened shea oleine in the rat at levels equating to approximately 7.5 g/kg/day.

Carthew *et al.* (2001) examined the carcinogenic potential of 15% (w/w) (approximately equivalent to 7.5 g/kg b.w./day) shea oleine (SO) in comparison with 15% (w/w) crude sheanut oil (SNO) and 15% (w/w) palm oil (PO) administered in the diet. The F_1 progeny (50 animals/sex/group) derived from an earlier reproduction study in Colworth-Wistar rats (Baldrick and Hepburn, 2000). Test diets were introduced at weaning (21 days) and were continued for 104 weeks. Analysis of the test materials revealed higher levels of unsaponifiable material in the SNO and SO (5 and 6.4%, respectively) as compared to the palm oil (0.1%); from this data, it can be estimated that animals consuming 7.5 g shea oleine/kg/day would have consumed up to 0.48 g/kg b.w./day (6.4%) of unsaponifiable matter. Mortality, clinical signs, body weights, food intake and clinical pathology were evaluated. In addition a complete necropsy examination was conducted at the conclusion of treatment, and a selected set of tissues/organs were collected for microscopic examination. Importantly, this study compared the three oils among themselves and not against a "control" chow.

Some isolated differences among the oils were observed. Final mortality values for both sexes were approximately 28 to 30% for the SO and SNO groups, and 40% for the PO group. No clinical signs were found in any animals that could be associated with a particular diet. Likewise, terminal body weights and mean food intake values were not significantly different among groups. Analysis of hematological parameters revealed a statistically significant reduction in the differential monocyte count, for male rats fed SO

($0.5x10^9$/l cf to $0.8x10^9$/l cf for PO), and females fed SNO and SO ($0.4x10^9$/l cf and $0.3x10^9$/l cf, respectively, to $0.6x10^9$/l cf for PO), though these changes were not considered to be of immunological significance. With respect to organ weights, mean absolute heart weights for both sexes fed SNO and SO diets were significantly reduced compared to the PO diet. Relative heart weights were also significantly reduced, although only for males fed SNO and SO. Mean relative liver weights were higher for female rats fed the SNO diet, however, the authors attributed this trend to the feeding of a high fat diet. There were no significant histopathological findings in rats of any group. Although pulmonary lipidosis (as indicated by focal accumulation of lipid-laden alveolar macrophages associated with thickening and increased cellularity of adjacent alveolar walls) was observed in both sexes of all diet groups, the highest incidence and severity was noted in the SO and SNO diet groups; thus, variations in pulmonary lipidosis were reported to be diet-related. However, the authors suggest that this finding may simply result from a naturally lower incidence of pulmonary lipidosis with palm oil diets. Tumor findings specific to the SNO and SO diets included a statistically significant increase in the number of hepatomas for females, pancreatic exocrine adenomas for males and skin keratoacanthomas for males. The authors suggested the observed increase in the incidence of hepatomas with treatment was related to the high fat content of the diets. In addition, the authors noted that the incidence of these tumor findings was similar to that given in the published data fro the Wistar rat, as well as in-house historical values.

Based on these findings, the authors concluded that compared to other commercially available edible oils, shea oleine showed no tumorigenic potential following dietary administration at 7.5 g/kg/day, or 0.48 g/kg/day of unsaponifiable material, in the rat.

In addition to the aforementioned preclinical safety data, two clinical studies attesting the safety of sheanut oil-derived materials were identified in the published scientific literature. Westrate and Meijer (1998) and Vissers *et al.* (2000) examined the effects of sheanut oil-derived substances on serum lipoprotein concentrations in humans. Although the data with regards to its effect on serum lipoprotein concentrations were inconclusive, both studies lend support to the safety of sheanut oil-derived substances in humans. Vissers *et al.* (2000) reported no adverse effects in healthy normocholesterolemic subjects treated with 2.6 g/day of triterpene alcohol intake from sheanut oil margarine for three weeks while a similar lack of adverse effects was seen by Westrate and Meijer (1998) in normocholesterolemic subjects consuming between 1.5 and 3.3 g/day sheanut oil-derived sterols for 3.5 weeks.

A third unpublished clinical study examined the effects of a sheanut oil preparation produced by the parent company of the manufacturer of the dietary ingredient on serum lipoprotein levels. Healthy normocholesterolemic and mildly hypercholesterolemic subjects (54 men, mean age 38.8 years, and 51 women, mean age 40.7 years) received either 30 g/day of a sheanut oil spread containing 3 g non-glycerides or c30 g/day of a sunflower oil spread as a control. The non-glyceride portion of the sheanut oil spread reportedly consisted of triterpene acetic acid esters, triterpene cinnamic acid esters, triterpene fatty acid esters, free triterpene alcohols, free sterols, and kariten. The mean

intake of triterpene alcohols from the sheanut oil spread was calculated to be 2.1 g/day. Researchers reported that the sheanut oil preparation was well tolerated and induced no clinically relevant adverse changes in blood chemistry or hematology. In addition, researchers reported significant reductions in plasma total- and LDL-cholesterol among patients treated with the sheanut oil preparation, which were reportedly reduced by 5% and 8%, respectively. Researchers suggested the hydrogenation and interesterification process employed in the manufacture of the test material led to an increased amount of triterpene alcohols in the unsaponifiable fraction and speculated that these contributed to the observed total and LDL-cholesterol-lowering effects.

Similarly, an unpublished, double-blind, randomized, placebo controlled, parallel group study was examined the analgesic and anti-inflammatory effects of BSP-201, as well as its safety and tolerance. Sixty healthy men received 3 or 6 g/day of BSP-201 or placebo for 22 days, dose levels that are equivalent to intakes of 1.5 and 3.0 g unsaponifiable material/day, respectively. BSP-201 was well tolerated and no treatment-related adverse events were observed. These findings support the other clinical and preclinical data that suggest that short-term intake of 6 g/day of BSP-201 (3.0 g/day of unsaponifiable material) could reasonably be expected to be safe.

Summary

As stated previously, sheanut-derived materials have a long history of use in humans, with no known adverse effects. The safety of the source material has been established, as sheanut oil was deemed GRAS by the United States Food and Drug Administration. In addition, shea oleine containing approximately 10% unsaponifiables (triterpenes and sterols) has reportedly been widely in baked goods and other foods in Europe without any reports of adverse effects, with the estimated daily intake of unsaponifiable matter amounting to more than 3 g/day in some cases. In addition, preclinical safety studies conducted by the manufacturer/distributor of the BSP-201 preparation containing 50% unsaponifiable matter and studies published in peer-reviewed scientific journals suggest that an intake of 3 g/day unsaponifiables from sheanut oil would reasonably be expected to be safe for a 70-kg adult. This value is 10- to 60-fold lower than amounts of unsaponifiable material used in subchronic and chronic experimental animal studies employing sheanut oil-derived substances (e.g., shea oleine), accounting for differences in species and length of exposure. It is further supported by a published clinical study in which 2.6 g/day of shea triterpene alcohols, the major constituents of shea unsaponifiable fraction and BSP-201, were administered. Use of the dietary ingredient according to conditions of use recommended or suggested in the labeling of the dietary supplement would result in a maximum daily intake of 3.0 g/day of unsaponifiable matter, a level that can reasonably be expected to be safe for a 70-kg adult based on the available data.